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A Phase I, Two-center Study of the Pharmacokinetics and Pharmacodynamics of Dexmedetomidine in Children

Guy C. Petroz, M.D.,* Nancy Sikich, R.N., B.Sc.N., M.Sc.,† Michael James, M.B., Ch.B., Ph.D., F.R.C.A., F.C.A.(SA),‡ Hanlie van Dyk, M.B., Ch.B., F.C.A.(SA),§ Steven L. Shafer, M.D.,‖ Markus Schily, M.B.,# Jerrold Lerman, M.D., F.R.C.P.C., F.A.N.Z.C.A.**

Background: **To investigate dexmedetomidine in children, the authors performed an open-label study of the pharmacokinetics and pharmacodynamics of dexmedetomidine.**

Methods: **Thirty-six children were assigned to three groups; 24 received dexmedetomidine and 12 received no drug. Three doses of dexmedetomidine, 2, 4, and 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$, were infused for 10 min. Cardiorespiratory responses and sedation were recorded for 24 h. Plasma concentrations of dexmedetomidine were collected for 24 h and analyzed. Pharmacokinetic variables were determined using nonlinear mixed effects modeling (NONMEM program). Cardiorespiratory responses were analyzed.**

Results: **Thirty-six children completed the study. There was an apparent difference in the pharmacokinetics between Canadian and South African children. The derived volumes and clearances in the Canadian children were V_1 = 0.81 l/kg, V_2 = 1.0 l/kg, Cl_1 (systemic clearance) = 0.013 $l \cdot kg^{-1} \cdot min^{-1}$, Cl_2 = 0.030 $l \cdot kg^{-1} \cdot min^{-1}$. The intersubject variabilities for V_1, V_2, and Cl_1 were 45%, 38%, and 22%, respectively. Plasma concentrations in South African children were 29% less than in Canadian children. The volumes and clearances in the South African children were 29% larger. The terminal half-life was 110 min (1.8 h). Median absolute prediction error for the two-compartment mammillary model was 18%. Heart rate and systolic blood pressure decreased with time and with increasing doses of dexmedetomidine. Respiratory rate and oxygen saturation (in air) were maintained. Sedation was transient.**

Conclusion: **The pharmacokinetics of dexmedetomidine in children are predictable with a terminal half-life of 1.8 h. Hemodynamic responses decreased with increasing doses of dexmedetomidine. Respiratory responses were maintained, whereas sedation was transient.**

This article is accompanied by an Editorial View. Please see: Fisher DM: Do the right thing (or do the market exclusivity thing?). ANESTHESIOLOGY 2006; 105:1074–5.

DEXMEDETOMIDINE is a selective α_2 agonist with sedative and analgesic properties. Dexmedetomidine has been studied extensively in adults in various settings and is approved by the US Food and Drug Administration for use in adults for less than 24 h.[1–7] In contrast to the clinical experience with dexmedetomidine in adults, the experience in children has been limited to anecdotal reports[8–10] and two randomized trials.[11,12] Preliminary data from a pharmacokinetic trial of dexmedetomidine in 10 postsurgical children in whom dexmedetomidine was infused for approximately 19 h indicated an elimination half-life of 2.65 h.[13] However, the safe use of dexmedetomidine in children requires an understanding of the pharmacokinetics and pharmacodynamics of a range of doses of dexmedetomidine in healthy children. To investigate the basic pharmacology of dexmedetomidine in children aged 2–12 yr, we undertook the following phase I, open-label study.

Materials and Methods

With approval by the local research ethics boards at the Hospital for Sick Children, Toronto, Canada, and at Red Cross War Memorial Children's Hospital, Cape Town, South Africa, and the federal regulatory authorities in the United States and Canada, 36 children, aged 2–12 yr, who were scheduled to undergo urologic, lower abdominal, or plastic surgery that required postoperative hospital admission for at least 24 h were enrolled in this phase I, controlled, open-label study. Written informed consent was obtained from the parents or guardians of each child. Assent was obtained from children older than 7 yr. Exclusion criteria included a history of serious head trauma or recent intracranial surgery, previous treatment with α_2 agonists or antagonist within the past 30 days, or treatment with enzyme-inducing medications or sedative medications (*e.g.*, phenobarbital, midazolam, antihistamines) within 12 h of surgery.

At each center, 18 children were sequentially assigned to three groups each containing 6 children. Within each group, a 10-min infusion of dexmedetomidine was administered to 4 of the children and no drug (control) was administered to the remaining 2, approximately 1 h before induction of anesthesia. The infusion of dexmedetomidine was prepared by diluting dexmedetomidine HCl (100 μg/ml, 2 ml base in 0.9% sodium chloride; Orion Pharma, Espoo, Finland). At the Toronto site, the 2 ml was diluted in 48 ml sodium chloride, 0.9%, for a

* Assistant Professor of Anaesthesia; The Hospital for Sick Children, University of Toronto. † Research Nurse; Department of Anaesthesia, St. Michael's Hospital, Toronto, Ontario, Canada. ‡ Professor and Chair, Department of Anaesthesia, University of Cape Town, Cape Town, South Africa. § Consultant Anaesthetist, Department of Anaesthesia, Red Cross War Memorial and Groote Schuur Hospitals, Cape Town, South Africa. ‖ Professor of Anesthesia, Stanford University, Stanford, California. Adjunct Professor of Biopharmaceutical Sciences, University of California at San Francisco, San Francisco, California. # Chef de service, Anesthésie Pédiatrique, Clinique pour enfants, Centre hospitalier, Biel-Bienne, Switzerland. ** Clinical Professor of Anesthesiology, Women and Children's Hospital of Buffalo, State University of New York, Buffalo, New York; and Strong Memorial Hospital, University of Rochester, Rochester, New York.

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Address correspondence to Dr. Petroz: Department of Anaesthesia, The Hospital for Sick Children, 555 University Avenue, Toronto M5G 1X8, Ontario, Canada. petroz@anaes.sickkids.on.ca.

final concentration of 4 μg/ml. At the Capetown site, the dexmedetomidine was diluted to a concentration of 2 μg/ml for most children and to a concentration of 4 μg/ml in several older children in the high dose group. The volume of diluted solution infused was recorded, although the concentration of dexmedetomidine in the solution was not assayed.

Children in group 1 who were scheduled to receive dexmedetomidine received a 10-min infusion of dexmedetomidine at 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (total dose 0.33 μg/kg), those in group 2 received a 10-min infusion at 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (total dose 0.66 μg/kg), and those in group 3 received a 10-min infusion at 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (total dose 1.0 μg/kg). Any study subject who did not receive the entire dose of dexmedetomidine or who did not complete all assessments was replaced. After completing each group of six children, the data were reviewed internally for safety before enrolling the next group.

On the day of surgery, two intravenous catheters were placed in those children who were scheduled to receive dexmedetomidine: one catheter to infuse dexmedetomidine and one to aspirate blood. The catheters were placed in different extremities. Approximately, 1 h before insertion of the cannulae, topical local anesthetic (EMLA; AstraZeneca, Wilmington, Delaware, or Ametop; Smith and Nephew, Lachine, Canada) was applied to two extremities. The intravenous catheters were placed with or without a brief exposure to 50% nitrous oxide in oxygen. In addition, 8% inspired sevoflurane was administered to children at the Capetown site to facilitate placement of the intravenous catheters. In those children, the inspired concentration of sevoflurane was reduced to 2% during intravenous catheter placement. The duration of sevoflurane administration for intravenous placement was 5–10 min. All anesthetics were discontinued as soon as the catheters were placed, and the children were permitted to recover before dexmedetomidine was administered. Children remained supine throughout the study period, breathing air. Approximately 1 h before induction of anesthesia, dexmedetomidine was infused intravenously using one calibrated syringe pump in each center for all of the children. The pumps were primed and pressurized to the steady state infusion rate before commencing the infusion. The infusion was delivered directly into a fast-flowing infusion as close as physically possible to the site of the catheter insertion into the vein.

Children who were assigned to the control group were monitored for approximately 1 h before and 23 h after induction of anesthesia in the same manner as those who received dexmedetomidine.

After observing the children for approximately 1 h, the children were transported to the operating room, where general anesthesia was induced using propofol and tracheal intubation was facilitated using rocuronium or vecuronium. Anesthesia was maintained throughout surgery with 70% nitrous oxide in oxygen and isoflurane as clinically required. Pain was managed with either a continuous epidural infusion of bupivacaine (without epinephrine) at a concentration and rate that were adjusted according to clinical response or intravenous opioids for at least 24 h postoperatively. Sedatives were avoided in the perioperative period, although analgesics were administered according to institutional pain guidelines. At the conclusion of surgery, neuromuscular blockade was antagonized, the anesthetic was discontinued, and the child was transported to the recovery room.

Monitoring and Data Collection

The electrocardiogram and pulse oximeter were monitored continuously throughout the 1-h observation period. Heart rate, systolic and diastolic blood pressures, respiratory rate, hemoglobin oxygen saturation, and temperature were recorded at baseline (immediately before the start of the dexmedetomidine infusion) and at 10, 15, 30, and 45 min and 1, 4, 8, 12, 16, 20, and 24 h after the start of the infusion. Heart rate was determined from the electrocardiographic display. A 12-lead electrocardiogram was recorded at baseline and 24 h after the infusion. Systolic and diastolic blood pressures were measured manually, using oscillotonometry, to minimize stimulation of the child. Respiratory rate, axillary temperature, and hemoglobin oxygen saturation were recorded throughout. Hemoglobin oxygen saturations less than 95% were reported as adverse events. Sedation was assessed using a four-point scale,[14] defined as 0 = appropriately asleep; 1 = awake and alert; 2 = drowsy but responds to stimulation; and 3 = very sedated, and was recorded from baseline until induction of anesthesia, at the same intervals as the other physiologic parameters.

Blood Sampling

Venous blood was collected for pharmacokinetic analyses from the 24 children who received dexmedetomidine. Ten blood samples (2 ml each) were collected at the following times: baseline (before administration of dexmedetomidine); 10 (end of infusion), 15, 30, 75, and 150 min; and 4, 6, 12, and 24 h after the start of the infusion. All heparinized blood samples were centrifuged within 30 min of collection, and the supernatant plasma was pipetted into glass vials and stored at −20°C until analysis. The frozen blood samples were transported to Abbott Park, Illinois, for analysis by the division of Drug Metabolism at Abbott Laboratories. A complete blood count, serum concentrations of electrolytes, creatinine, urea, and proteins, and liver function tests were performed at baseline and at 24 h in all 24 children.

Pharmacokinetic Analysis

The concentration of dexmedetomidine in plasma was analyzed using a validated gas chromatography–mass

Table 1. Summary of Subject Demographics

	Group 1		Group 2		Group 3	
	Control (n = 4)	Dex 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 8)	Control (n = 4)	Dex 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 8)	Control (n = 4)	Dex 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 8)
Age, yr	8.8 ± 2.1 (6–11)	4.1 ± 2.4 (2–8)	5.3 ± 4.3 (2–11)	6.4 ± 2.7 (3–11)	6.5 ± 5.3 (2–12)	6.3 ± 2.8 (3–11)
Height, cm	136.5 ± 16.9 (115–154)	104.4 ± 15.3 (84–124)	111.8 ± 26.7 (89–143)	115.6 ± 18.1 (90–143)	102.0 ± 28.6 (84–135)	114.4 ± 15.5 (91–138)
Weight, kg	33.1 ± 10.5 (22–47)	16.8 ± 5.2 (10–26)	22.0 ± 10.4 (12–35)	20.5 ± 6.8 (14–33)	20.9 ± 10.7 (12–31)	22.7 ± 9.3 (12–42)

Values are mean ± SD (range).
Dex = dexmedetomidine.

spectrometry method. The lower limit of detection of dexmedetomidine was 10 pg/ml (0.010 ng/ml).

The calibration curve for the plasma concentration of dexmedetomidine contained five standards that ranged between 10.0 and 1,500 pg/ml. The correlation values for all calibration curves were greater than 0.996. Samples quantified below the lowest standard were reported as zero. In-study quality control samples, supplemented with concentrations of 20, 600, and 1200 pg/ml of dexmedetomidine, were analyzed with the unknowns. The coefficient of variation for the analyses ranged between 7.1% and 11.7%.

The *in vitro* protein binding for [^{3}H]dexmedetomidine was determined in the baseline plasma samples obtained from 11 of the children using an ultrafiltration technique.

The pharmacokinetic analysis was performed using the software program NONMEM.[15] One-, two-, and three-compartment mammillary models were considered. The models were explored for covariate effects, including age, weight, and study site (Canada *vs.* South Africa). Parameters were considered statistically significant if the addition of a single parameter to the model decreased the log likelihood value by 3.84 (chi-square value for $P < 0.05$, 1 degree of freedom). The volumes and clearances were assumed to be log-normally distributed in the population, as was the residual intraindividual variability. NONMEM was run using the "first order conditional estimation" method.

Goodness of fit was assessed graphically and using the prediction error, defined as (measured − predicted)/predicted. Median prediction error and median absolute prediction error were calculated using the optimal NONMEM model.

Pharmacodynamic Analysis

Heart rate, systolic and diastolic blood pressures, respiratory rate, and hemoglobin oxygen saturation were compared over time with baseline and among the dosing groups using two-way analysis of covariance with repeated-measures and the Dunnett test for *post hoc* comparisons. Main and interaction effects were identified. $P < 0.05$ was accepted as the threshold for statistical significance.

The consent rate in the Toronto site was calculated as the ratio of the number of consents to the total number of parents who were contacted for enrollment in the study.

Results

Thirty-six children completed the study, 18 at each center. There were no dropouts. Demographic data are summarized in table 1.

Figure 1 shows the concentration-*versus*-time data for all children in the South Africa (top graph) and Canada (bottom graph) groups. The three lines represent the NONMEM fits for doses of 2, 4, and 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine. Measurable concentrations of dexmedetomidine were present up to 360 min in all subjects. However, from 720 min forward, there was only a single plasma concentration above the limit of detection. For this reason, the pharmacokinetic analysis was limited to the first 360 min of data.

The plasma protein binding (mean ± SD) of dexmedetomidine was 92.6 ± 0.7% with a free fraction of 7.4 ± 0.7%.

In general, the plasma concentrations in the Canadian children were approximately 30% greater than those in the South African children. The difference, as estimated by NONMEM, was 29%. The difference, based on the log average ratio of dose normalized concentrations in each population at each time point in the protocol, was 33%.

Table 2 presents the volumes and clearances estimated by NONMEM. The best model that characterized the data was a two-compartment mammillary model, which was preferred over the otherwise identical one-compartment model by an improvement in −2 log likelihood of 57 points. Weight was a significant covariate, as was the study center: Canada or South Africa. The "South African proportionality," 1.29, was the factor by which the volumes and clearances in the South African children exceeded those in the Canadian children.

The "approximate coefficient of variation" (table 2) is

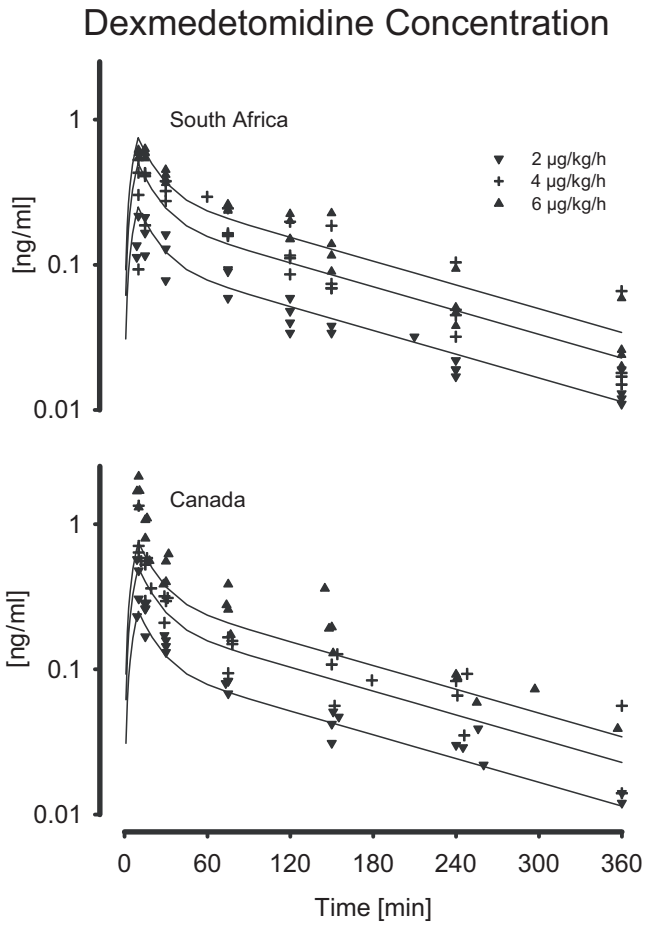

Fig. 1. Venous plasma concentrations of dexmedetomidine *versus* time (24 h) for three doses: 2 (▼), 4 (+), and 6 (▲) $\mu g \cdot kg^{-1} \cdot h^{-1}$ infused for 10 min (corresponding to 0.33, 0.66, and 1.0 µg/kg dexmedetomidine) (n = 4 children per group per center) for South African children (*top*) and Canadian children (*bottom*). The concentrations of dexmedetomidine in the Canadian children were on average greater than those in the South African children. The *lines* are the predicted plasma concentrations for each group, at each dose.

the SD in the log domain, which is approximately the coefficient of variation in the standard domain. V_1, the central volume distribution, had the largest subject-to-subject variability, approximately 45%, whereas Cl_1, the systemic clearance, had the smallest subject-to-subject variability, approximately 22%. NONMEM was unable to estimate intersubject variability of Cl_2.

The "derived" parameters (table 2) are the micro rate constants, exponents, fractional coefficients (sum to 1) of the unit disposition function, and true coefficients of the unit disposition function, as derived from the volumes and clearances estimated by NONMEM.

Figure 2 illustrates the measured/predicted concentrations for all children based either on the typical values estimated by NONMEM for the population (*i.e.*, those shown in table 2) (top graph) or the individual *post hoc* Bayesian estimate of volumes and clearances in each child (bottom graph). The fit was unbiased, with a median prediction error of −2.6%, and reasonably accurate, with a median absolute prediction error of 18%.

Figure 3 illustrates the context sensitive decrement times for decrements of 80%, 50%, and 20% in the plasma concentrations of dexmedetomidine. After steady state infusions of 2 h, little additional time is required for the plasma concentrations of dexmedetomidine to decrease when the infusion is terminated. Figure 4 shows the infusion rate over time that would be required to maintain a plasma dexmedetomidine concentration of 0.3 ng/ml, based on the optimal pharmacokinetic model.

Heart rate decreased (≤ 15% compared with baseline) significantly in response to dexmedetomidine during the first hour after infusion (fig. 5). Overall, heart rate decreased as the dose of dexmedetomidine increased ($P < 0.00008$) and with time ($P < 0.025$), independently. The interaction, dose × time, did not exert a significant effect. Heart rate decreased to a greater extent with larger doses of dexmedetomidine (fig. 5), *i.e.*, the decreases in heart rate after 4 and 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine overall ($P = 0.038$ and 0.0002, respectively) were significantly greater than the decreases after control and 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Two children, aged 10 and 11 yr, whose baseline heart rates were 50–60 beats/min (fig. 5), maintained similar heart rates during the observation period and were not treated.

Systolic blood pressures decreased (≤ 25% compared with baseline) significantly in response to dexmedetomidine during the first hour after infusion (fig. 6A). Overall, systolic blood pressure decreased as the dose of dexmedetomidine increased ($P = 0.028$) and with time ($P = 0.029$) independently, although the interaction, dose × time, had no effect. The dose 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ exerted a significant ($P = 0.038$) overall effect on systolic blood pressure compared with baseline. Diastolic blood pressure decreased significantly after the infusion of dexmedetomidine (fig. 6B). Overall, diastolic pressure decreased significantly with time ($P = 0.02$), although the dose of dexmedetomidine and the interaction, dose × time, did not exert significant effects. There was one instance of hypertension that was described as an adverse event during the first hour after infusion of dexmedetomidine. This is detailed below.

Mean changes in heart rate and systolic blood pressure from baseline during the 24-h monitoring period are shown in figure 7. Mean heart rate decreased for the first hour after infusion at all three doses of dexmedetomidine, although heart rate in the control group was maintained. During general anesthesia and surgery, heart rate predictably increased, after which it returned toward baseline. Mean systolic blood pressure decreased during the first hour after infusion but then returned to baseline or above during the perioperative period. The contribution of surgical stimulation and postoperative pain to the hemodynamic responses could not be determined.

Table 2. Pharmacokinetics of Dexmedetomidine

Parameters	Typical Value	SE, %	Approximate Coefficient of Variation
Estimated			
Volumes			
V_1, l/kg	0.81	15	0.45
V_2, l/kg	1.00	12	0.38
Clearances			
Cl_1, $l \cdot kg^{-1} \cdot min^{-1}$	0.013	8	0.22
Cl_2, $l \cdot kg^{-1} \cdot min^{-1}$	0.030	10	
South Africa proportionality	1.29	11	
Derived			
Micro rate constants			
k_{10}, min^{-1}	0.016		
k_{12}, min^{-1}	0.037		
k_{21}, min^{-1}	0.030		
Exponents			
α, min^{-1}	0.076		
β, min^{-1}	0.0063		
Half-lives			
α, min	9		
β, min	110		
Fractional coefficients			
A	0.66		
B	0.34		
True coefficients			
A, l^{-1}	0.82/Proportionality		
B, l^{-1}	0.41/Proportionality		

V_1 is the central volume of distribution; V_2 is the peripheral volume of distribution; Cl_1 is the systemic clearance (metabolism and renal excretion); Cl_2 is the distribution clearance (between V_1 and V_2); South Africa proportionality is the factor by which the volumes and clearances in South African children exceeded those in Canadian children, as a result of lower plasma concentrations in the South African children; k_{10}, k_{12}, and k_{21} are the rate constants that define the rate of transfer from one compartment to another compartment in the mammillary model; half-lives are the early phase, α, and the terminal phase, β; the concentration–time curves are expressed as the plasma concentration $= A \times e^{-\alpha t} + B \times e^{-\beta t}$, where A and B are the true coefficients and α and β are the exponents; fractional coefficients A and B are the individual true coefficients divided by the sum of the true coefficients.

Respiratory rate did not change significantly during the first hour after dexmedetomidine at any dose including the control group (fig. 8). Time, the dose of dexmedetomidine, and the interaction, dose × time, did not significantly affect the respiratory rate.

Hemoglobin oxygen saturation did not change significantly during the first hour after infusion of dexmedetomidine (fig. 9). Time, the dose of dexmedetomidine, and the interaction, dose × time, did not significantly affect the hemoglobin oxygen saturation. Hemoglobin oxygen saturation decreased to 94% transiently in three of the children. Two of these were reported as adverse events, but all three episodes are described below in the Results.

Most children became sedated several minutes after the infusion of dexmedetomidine commenced (fig. 10). The duration of the sedation was variable as shown in the figure, although most children could be aroused by tapping the glabella. Some of the children recovered from their sedation by 30–40 min after infusion, became upset, and began to cry. We sedated some of these children with propofol and transferred them to the operating room to begin their anesthetic. The use of propofol precluded further measurements of sedation and decreased the number of children who were evaluable for sedation toward the end of the first hour after infusion.

Laboratory tests including electrocardiograms did not change before and after the study in any children.

Dexmedetomidine was well tolerated in this study. No serious adverse events between the start of the infusion of dexmedetomidine and induction of anesthesia were attributable to dexmedetomidine. However, three adverse events were reported. In the first two events, the hemoglobin oxygen saturation decreased in two children transiently to 94% during the infusion of dexmedetomidine. In the first, hemoglobin oxygen saturation decreased after the child had received 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 10 min. The saturation improved after the child was encouraged to cough and expectorate oral secretions. In the second, the hemoglobin oxygen saturation decreased without an obvious cause after the child had received 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 10 min. This child was well-sedated and may have experienced some respiratory depression that resulted in a saturation of 94% while breathing room air. In the third adverse event, the child was noted to be hypertensive, with a blood pressure of 121/95 mmHg at 5 min after completion of the dexmedetomidine infusion. This child was anxious and crying while the blood pressure was being measured. The hypertensive measurement was a single transient measurement. A fourth episode, which was not reported as an adverse event, occurred in a child who had received 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine for 10 min. The hemoglobin oxygen saturation decreased while the child was crying but improved as soon as the crying abated.

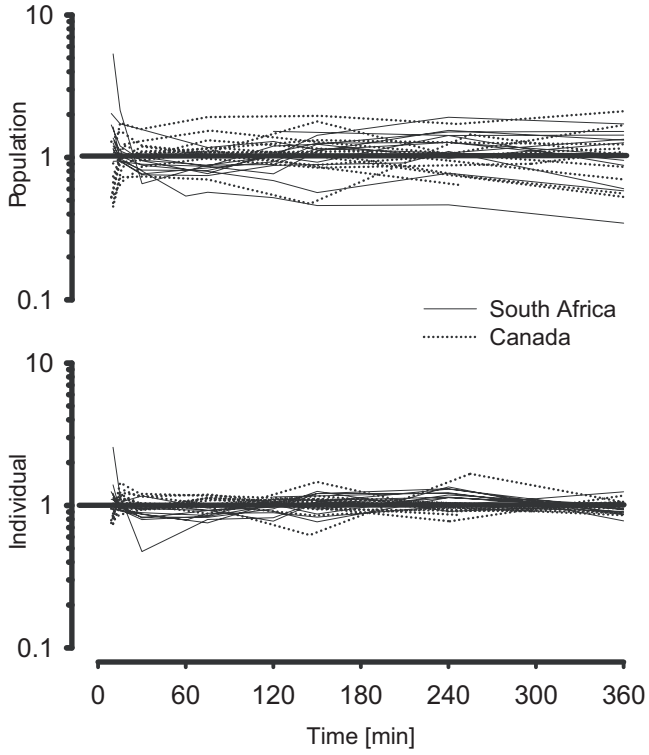

Fig. 2. The measured/predicted plasma concentrations of dexmedetomidine *versus* time for the best model estimated by NONMEM, based on the typical values (population model, *top*), and the individual *post hoc* Bayesian estimates of volume and clearance in each child (individual models, *bottom*). The line of unity appears as a *solid horizontal line* in both graphs. Overall, the quality of the fit was quite good, with little suggestion of model misspecification.

This episode was deemed unrelated to dexmedetomidine and was not reported as an adverse event.

Seven serious adverse events occurred after induction of anesthesia. None of these events were attributed to dexmedetomidine by the local investigator. The events

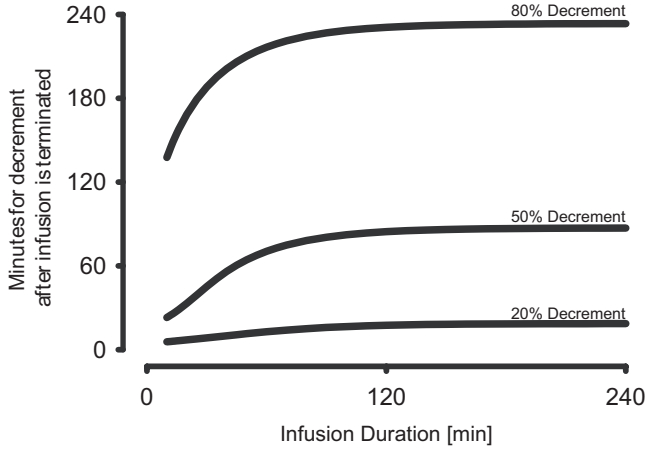

Fig. 3. Context sensitive decrement times for pseudo–steady state infusions up to 240 h, showing decrements of 80%, 50% (the "context-sensitive half-time"), and 20%. After an hour of infusing dexmedetomidine, there is no significant additional accumulation of drug, resulting in flat decrement time–*versus*–infusion duration curves beyond 1 h.

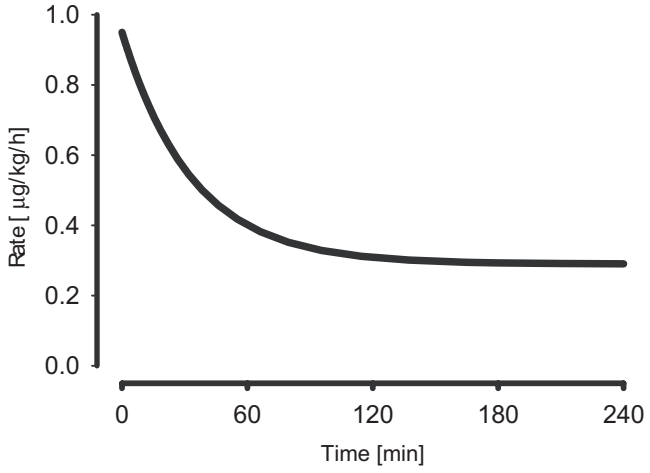

Fig. 4. Infusion rate over time for maintaining a plasma dexmedetomidine concentration of 0.3 ng/ml, based on the optimum NONMEM model.

were as follows: anemia, infection, hydronephrosis and abnormal renal function, diarrhea, fever, dehydration, infection, cellulitis, right bundle branch block, and hemorrhage. All children recovered uneventfully.

The rate of consent to participate in this study was 5% in Toronto. Similar data were not available from South Africa.

Discussion

We undertook this phase I, open-label study of the pharmacokinetics and pharmacodynamics of dexmedetomidine after a single 10-min infusion in healthy children aged 2–12 yr to lay the foundations for a scientific basis for the use of dexmedetomidine in children and to provide a framework to design future studies with dexmedetomidine.

We found that using a two-compartment mammillary model, the pharmacokinetics of dexmedetomidine in children are similar to those reported previously in adults[2,5,7,16] and in a preliminary study in children after surgery.[13] Total plasma protein binding of dexmedetomidine in children, 92.6%, is similar to that reported in adults.[17] Weight-adjusted mean total body clearance, Cl_1, $0.013\ l \cdot kg^{-1} \cdot min^{-1}$, and the volume of distribution of the peripheral compartment, V_2, 1.0 l/kg, are similar (within 30–40%) to those reported previously in adults and in children after surgery.[1,2,7,13,16] There was no evidence of dose-dependent kinetics in this study, which is also consistent with previous data in adults.[7] The terminal half-life in the current study, 1.8 h, is similar to that reported previously in adults but one third less than that reported in a preliminary study of children after surgery after a prolonged infusion of dexmedetomidine.[1,2,7,13,16] Pharmacokinetic modeling of dexmedetomidine yielded a mean absolute prediction error of 18%, which is as small an error as that published for remifen-

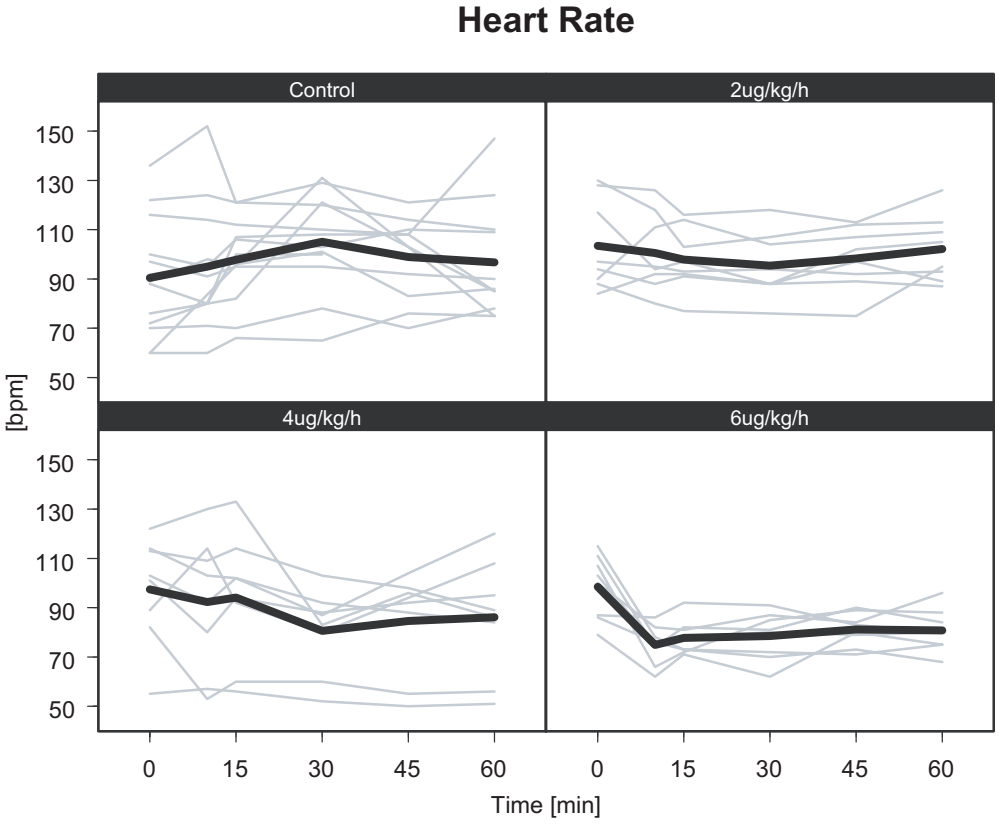

Fig. 5. Heart rate responses for each child and the mean during the first hour after control (0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and infusions of 2, 4, and 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine for 10 min (corresponding to 0, 0.33, 0.66, and 1.0 μg/kg). In each frame, mean heart rate response is represented by the *heavy line* and individual responses are represented by the *light lines*. Overall, the dose of dexmedetomidine ($P < 0.00008$) and time ($P < 0.025$) independently decreased the heart rate. Heart rate decreased to a greater extent with larger doses of dexmedetomidine, *i.e.*, the decreases in heart rate after 4 and 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine overall ($P = 0.038$ and 0.0002, respectively) were significantly greater than the decreases after control and 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$. bpm = beats/min.

tanil.[18] These results suggest that the pharmacokinetics of a single dose of dexmedetomidine in healthy children are predictable and similar to those in adults.

We cannot explain the difference in the volumes and clearances between the Canadian and South African children (table 2). To fit our data to a single model, despite the lower concentrations observed in the South African children, we applied a correction factor to the volumes and clearances in that population. Although this approach to modeling the data implies a true biologic mechanism, we believe that this is an improbable, although not impossible, conclusion. In our view, the most likely explanation is that the South African children received 29% less dexmedetomidine than the Canadian children for some technical reason. Alternatively, a systematic error in sample handling may have resulted in a 29% loss of the drug from the South African samples. The 29% difference was systematic, as evidenced by the small residual error for the population model (fig. 2) and examination of the goodness-of-fit plots. Our conclusion is that this 29% difference is an artifact of the drug administration and/or sample handling and does not reflect a true pharmacokinetic difference between the populations. However, we cannot absolutely rule out the possibility of a true biologic explanation.

Heart rate and systolic blood pressure decreased modestly ($\leq$ 15% and $\leq$ 25%, respectively) but steadily during the first hour after dexmedetomidine (figs. 5, 6A, and 7). These hemodynamic responses to an infusion of a single dose of dexmedetomidine over 10 min are consistent with published data.[1,5,7,16,19] The magnitude of the decreases in heart rate and systolic blood pressure during the first hour after infusion increased as the dose of dexmedetomidine increased. These circulatory responses to dexmedetomidine limit the speed at which dexmedetomidine may be infused and the magnitude of the dose.[15,17] These heart rate and blood pressure responses have been attributed to a decrease in central sympathetic tone and an increase in vagal activity in adults, although we did not measure the catecholamine responses to dexmedetomidine in this study.[4,6] In the current study, the decreases in heart rate and systolic blood pressure were of modest clinical interest and, at least in this setting, did not warrant corrective action with vasoactive drugs.

Transient hypertension was observed in one child im-

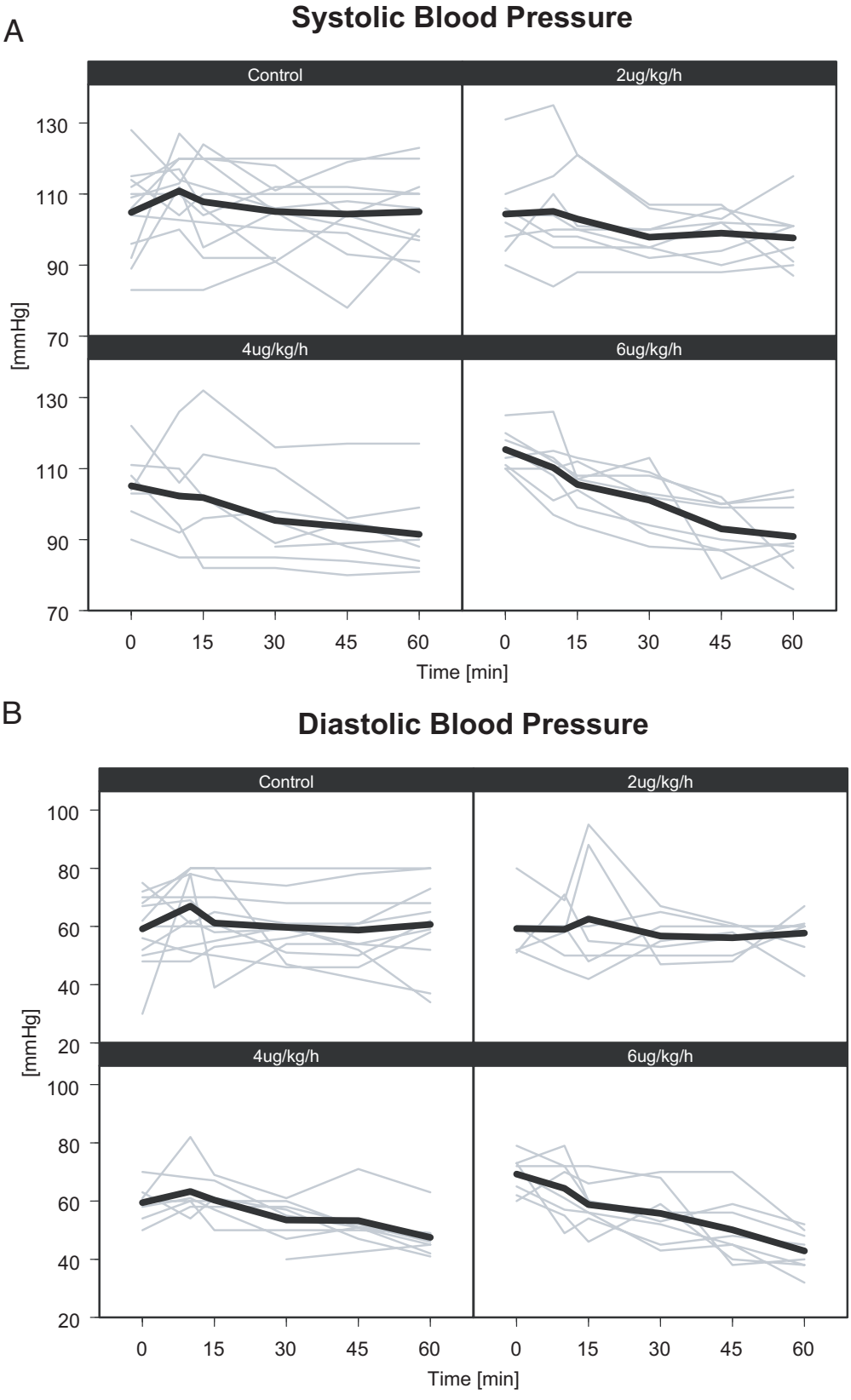

Fig. 6. Systolic systemic blood pressure (*A*) and diastolic systemic blood pressure (*B*) during the first hour after control (0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and infusions of 2, 4, and 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine for 10 min (corresponding to 0.33, 0.66, and 1.0 $\mu g/kg$). In each frame, mean systolic or diastolic response is represented by the *heavy line* and individual responses are represented by the *light lines*. Overall, the dose of dexmedetomidine ($P = 0.028$) and time ($P = 0.029$) independently decreased systolic blood pressure during the first hour after infusion, but the interaction, dose × time, had no effect. Systolic pressure decreased 25% or less during the observation period. The effect of 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ differed significantly from the other three ($P = 0.038$).

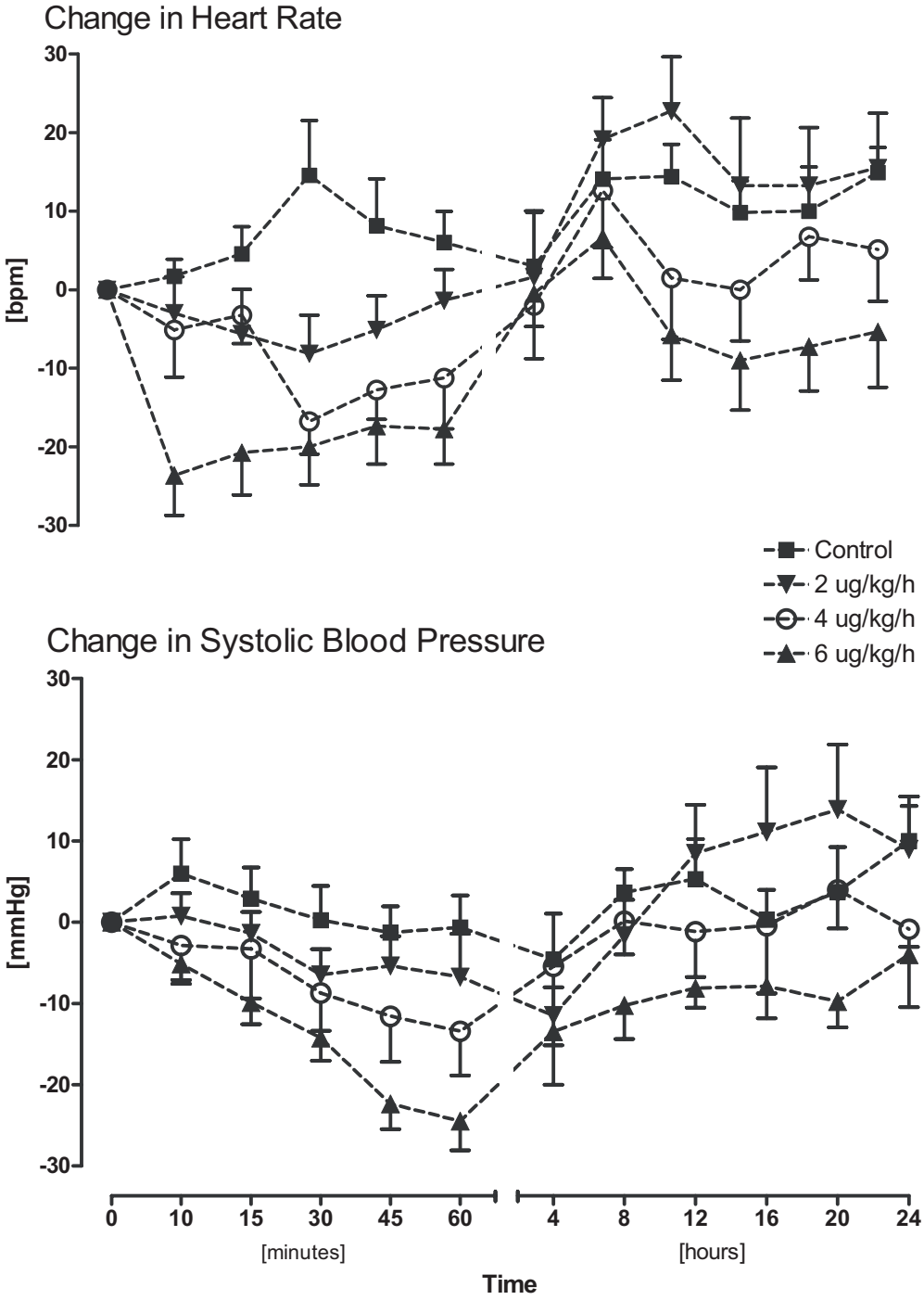

Fig. 7. Mean (± SD) change in heart rate (*top*) and systolic blood pressure (*bottom*) from baseline (before dexmedetomidine infusion) for the four doses: control (0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and infusions of 2, 4, and 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine (for 10 min) (corresponding to 0.33, 0.66, and 1.0 $\mu g/kg$) recorded for 24 h. General anesthesia and surgery occurred between 1 and 4 h.

mediately after dexmedetomidine, although it is difficult to attribute the hypertension to dexmedetomidine because the child was crying and thrashing about during the recording. Whether this was a true recording of hypertension or an artifact remains unclear. In adults, the circulatory responses to dexmedetomidine are biphasic with a transient increase in systolic blood pressure and a decrease in heart rate followed by return of the variables toward baseline.[1,4] This transient, sympathetic-like response was not noted in the current study for several plausible reasons, including that dexmedetomidine was infused over 10 min, continuous blood pressure monitoring was not performed, and it may not be a feature of dexmedetomidine in children. These circulatory responses to dexmedetomidine suggest that vital signs should be monitored frequently, at least during the

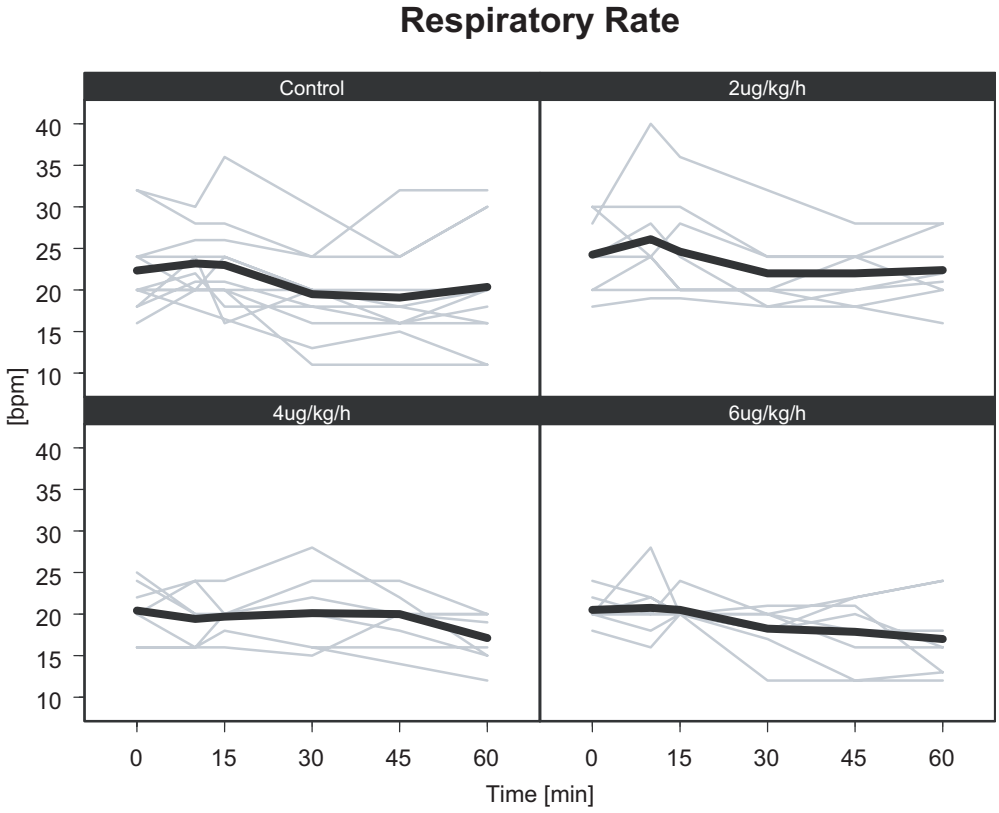

Fig. 8. Respiratory rate during the first hour after control (0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and infusions of 2, 4, and 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine (corresponding to 0.33, 0.66, and 1.0 μg/kg) for 10 min. In each frame, mean respiratory response is represented by the *heavy line* and individual responses are represented by the *light lines*. Respiratory rates did not change significantly throughout the period of observation. bpm = breaths/min.

early phases of sedation, to avoid precipitous interactions with anesthetics in children who are sedated with dexmedetomidine.

We reported the changes in heart rate and systolic blood pressure from pre-dexmedetomidine values for 24 h after the start of the dexmedetomidine infusion to provide a complete description of the cardiovascular responses to dexmedetomidine, recognizing that for much of the 24 h, these responses could not be directly attributed to dexmedetomidine (fig. 7). During the first hour after dexmedetomidine, the cardiorespiratory responses were attributable to the dexmedetomidine because it was the sole anesthetic administered in the absence of surgical simulation. After the first hour, general anesthesia was administered without rigid control of the heart rate and blood pressure. During and after surgery, pain was controlled with either a caudal/epidural block or intravenous opioids according to the patient and surgical requirements. Pain control was targeted to institutional guidelines. As a consequence, we found it difficult to isolate the effects of dexmedetomidine on heart rate and blood pressure in the postoperative period from those of surgery, residual general anesthesia, and pain. Based on the pharmacokinetic data, the plasma concentrations of dexmedetomidine after 6 h in this study were below the detectable limit of the assay. With a terminal half-life of 1.8 h, the plasma concentrations of dexmedetomidine 8 h or more after the infusion were unlikely to have substantively contributed to the cardiovascular responses. Although it is unlikely that the cardiovascular responses after surgery and up to 24 h after dexmedetomidine were affected by the dexmedetomidine dosing, we believed that it was important to report these data in the event an interaction between dexmedetomidine and these anesthetic/analgesic drugs might be identified at a later date.

The respiratory responses to all three doses of dexmedetomidine in the current study were minimal.[3,6,7,20] Consistent with adult data, we found that respiratory rate was maintained at all doses of dexmedetomidine and unchanged compared with that in the control group (fig. 8). Similarly, the hemoglobin oxygen saturation was maintained during sedation with dexmedetomidine even though the children were supine and breathed only air. The hemoglobin oxygen saturation decreased transiently to 94% in three children, without sequelae. In two of the three children, the desaturation was attributed to a combination of the effect of dexmedetomidine sedation and mild hypoventilation while breathing air. Similar instances of desaturation have not been reported previously in either

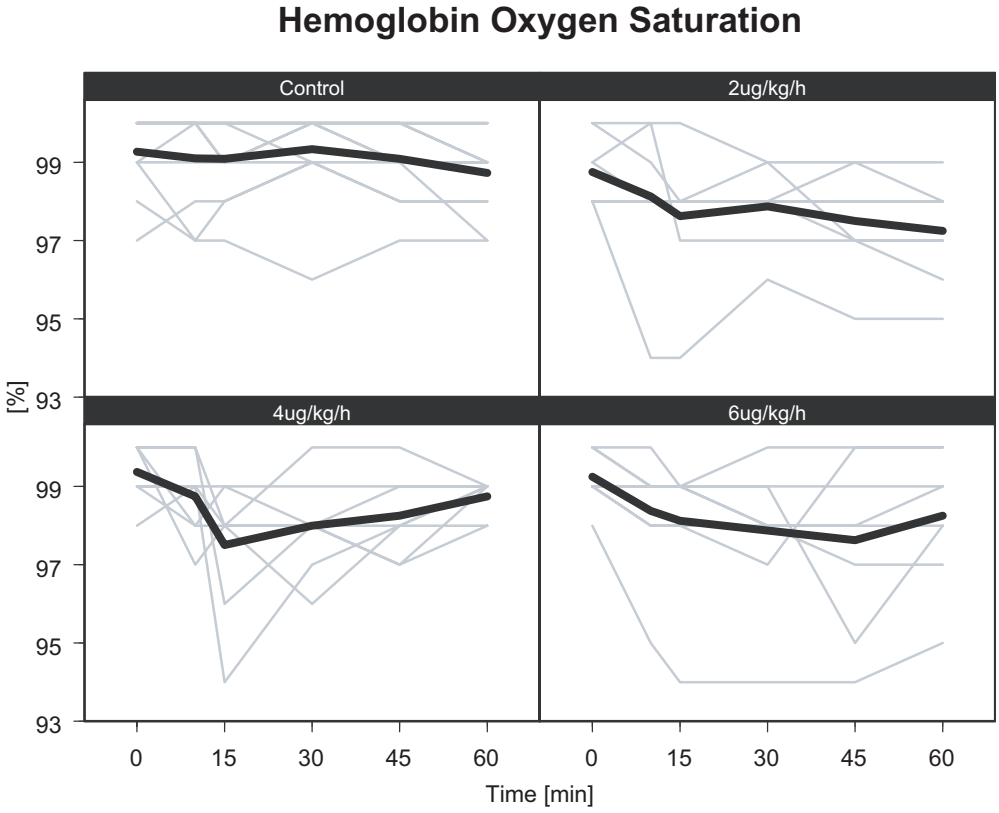

Fig. 9. Hemoglobin oxygen saturation during the first hour after control (0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and infusions of 2, 4, and 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine for 10 min (corresponding to 0.33, 0.66, and 1.0 $\mu g/kg$). In each frame, mean hemoglobin oxygen saturation is represented by the *heavy line* and individual responses are represented by the *light lines*. Hemoglobin oxygen saturation did not change significantly during the observation period. Hemoglobin saturation decreased transiently to 94% in three children who were breathing room air. These three events are discussed in the Results.

adults or children who were sedated with dexmedetomidine.[3,5,6] This warrants further investigation.

Dexmedetomidine sedated the children in this study to varying degrees and for varying periods of time. This is consistent with the sedative effects of dexmedetomidine in adults[3,5–7] and children.[8–12] Dexmedetomidine produces a different quality of sedation than other sedative medications, because it effects sedation *via* α_2 receptors, by attenuating sympathetic activity and the level of arousal. Our data do not suggest dose-dependent sedation in response to dexmedetomidine, although the sample size in this study was small and the quality of the sedation scale precludes a detailed comparison of the extent of sedation. In adults, however, published data support dose-dependent sedation after dexmedetomidine.[3,5–7] Until additional data are forthcoming, the relation between the dose of dexmedetomidine and depth of sedation in children remains unclear.

Interactions between dexmedetomidine and other medications may affect the pharmacokinetics and cardiorespiratory effects of these medications. For example, published data in humans show that dexmedetomidine decreases the volume of distribution and clearance of sodium thiopental. This has been attributed to a decrease in cardiac output and regional blood flow.[21] In dogs, dexmedetomidine exacerbates fentanyl-induced bradycardia.[22] Although comparable data are unavailable in children, bradycardia has been reported after dexmedetomidine in an infant who had been treated with digoxin.[23] Neither the pharmacokinetics of nor the cardiorespiratory responses to dexmedetomidine in infants have been elucidated to date. Until further data are available, caution should be exercised when dexmedetomidine is combined with medications that may decrease heart rate and blood pressure, particularly in neonates and infants.

We designed this phase I trial to characterize the pharmacology of dexmedetomidine in children after considering the potential risks and side effects of dexmedetomidine in children and balancing these with the potential benefits of the data we sought to collect. In the absence of data for dexmedetomidine in children, we adopted a cautious study design by beginning with a low dose of dexmedetomidine, by completing enrollment in each dose before beginning enrollment in the next dose, by evaluating and reporting the results of each treatment dose for safety and side effects to the Food and Drug Administration before increasing the dose administered and by including every third child as a control.

In summary, we investigated the pharmacology of a

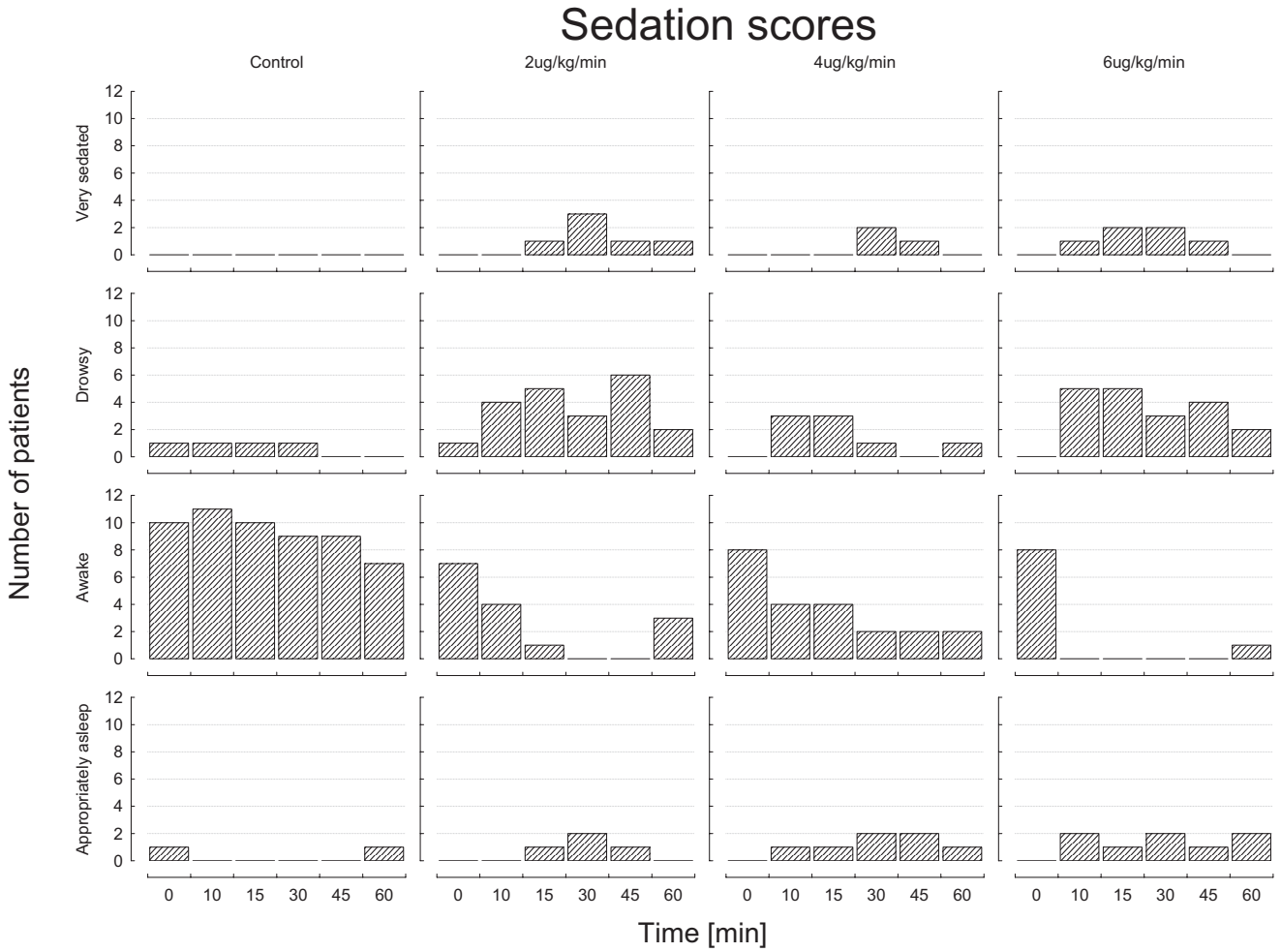

Fig. 10. Sedation scores during the first hour after control (0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and infusions of 2, 4, and 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine for 10 min (corresponding to 0.33, 0.66, and 1.0 μg/kg). Transient sedation occurred in children at all three doses of dexmedetomidine, although the small numbers of children and the sedation scale that was used precluded establishing a dose–response relation. Some children recovered from their sedation before the end of the hour and were sedated with propofol or were taken directly to the operating room for surgery. These children were no longer evaluated for dexmedetomidine sedation; hence the number of evaluable children diminished toward the end of the observation period.

single intravenous dose of dexmedetomidine, between 0.33 and 1.0 μg/kg, in healthy children. The pharmacokinetics of dexmedetomidine in children were predictable, with a median error of 18% and a terminal half-life of 1.8 h. Heart rate and systolic blood pressure decreased modestly with increasing doses of dexmedetomidine and with time during the first hour after dexmedetomidine, whereas respiratory variables were maintained. Transient sedation occurred at all doses of dexmedetomidine.

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